Update on clinical and radiological staging and surveillance of bladder cancer

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Numerous investigations are required during the course of diagnosis, staging, and surveillance of bladder neoplasms. Improvements in the clinical maneuvers that have traditionally been performed on bladder cancer patients may facilitate a more precise determination of tumor stage or the presence of recurrence. New techniques for assessing patients hold promise for more accurate diagnosis and follow-up. This article reviews some of the advances in clinical and radiologic investigations for staging and surveillance of bladder cancer patients, including the tumor, node, metastasis (TNM) staging system; protocols for staging bladder cancer and follow-up of patients after treatment; methods of surgical resection and pathologic examination; fluorescence cystoscopy; virtual cystoscopy; positron emission tomography; and ultrasmall superparamagnetic iron oxide magnetic resonance imaging.

Key Words: bladder cancer, surveillance, staging

Introduction

Patients undergo numerous maneuvers during the course of diagnosis and staging of their bladder cancers. Following treatment, they frequently have repeated investigations to monitor for cancer recurrence. In recent years, new methods for staging and performing surveillance of bladder cancer patients have been investigated and proposed. These hold promise for improvement on current techniques. In addition, data has emerged regarding the clinical maneuvers that have traditionally been performed in assessing bladder cancer patients, such as surgical resection and pathologic examination. An improved understanding of their potential pitfalls will facilitate more precise determination of tumor stage or the presence of cancer in patients being observed for evidence of recurrence.

This article summarizes advances in current and emerging clinical and radiologic investigations for staging and surveillance of bladder cancer patients. Areas that will be covered include the tumor, node, metastasis (TNM) staging system; protocols for staging bladder cancer and follow-up of patients after treatment; methods of surgical resection; pathologic examination; fluorescence cystoscopy; virtual cystoscopy; positron emission tomography (PET); and ultrasmall superparamagnetic iron oxide magnetic resonance imaging (USPIO MRI).

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Advances in clinical and radiologic staging and surveillance

TNM staging system

The most commonly used method for staging bladder cancer is the TNM staging system, published by the Union Internationale Contre le Cancer (UICC), as well as the AJCC (American Joint Committee on Cancer). The TNM system undergoes changes every few years. The most recent version is the sixth edition, published in 2002.[1] For bladder cancer, there was no change between the prior fifth edition published in 1997[2] and the current version, but earlier editions varied substantially. Because changes do occur in the TNM system over time, it is important to use the most up-to-date version if possible, and to specify the version used, so that clinical data is communicated accurately.

In order to stage patients with bladder cancer, four modalities are currently used in the TNM system. These are: physical examination, imaging, endoscopy, and pathology. Unlike testis cancer, where serum molecular markers are included as one of the staging maneuvers, urine molecular markers are not currently included as part of bladder cancer staging. The bladder cancer staging system will undoubtedly undergo further changes in the future,[3] and urinary markers may eventually comprise one of the staging investigations.

Clinical protocols and practice guidelines

There are a number published protocols for follow-up and staging of bladder cancer.[4-7] One comprehensive, easily accessible, and updated set of consensus clinical guidelines comes from the National Comprehensive Cancer Network (NCCN) in the United States. The NCCN is a non-profit organization comprised of 19 U.S. cancer centers. Its purpose is to provide information to patients and health professionals regarding cancer care. To this end, it has developed clinical practice guidelines that are available on the World Wide Web at http://www.nccn.org/professionals/physician_gls/default.asp. They can also be obtained on a freely distributed CD-ROM that may be ordered from this website.

In the NCCN bladder cancer clinical practice guidelines, the pre-operative staging workup depends in part of the cystoscopic appearance of the tumor – that is, whether the urologist thinks a tumor is likely to be muscle invasive. For what are thought to be likely muscle-invasive tumors, an abdominopelvic CT should be obtained prior to TURBT, as the CT scan is of greater importance for determining management with these tumors. It is known that if CT is performed after endoscopic resection, there is a risk of inducing a false upstaging of the tumor appearance, due to the resultant post-surgical inflammatory response.[8]

Following endoscopic resection, for tumors being managed without cystectomy, the NCCN guidelines for low risk cancers suggest less frequent cystoscopic surveillance, which has also been suggested by others.[9,10] Furthermore, upper tract imaging is not mandated; there is evidence that the risk of developing upper tract tumors is low when the bladder tumor is solitary, low stage, and low grade.[11] For higher risk cancers managed without cystectomy, the frequency of cystoscopy is increased, and upper tract imaging is required. Recent data suggests that adherence to surveillance cystoscopy schedules is suboptimal in a large proportion of cases.[12] About 18% of patients undergo less than one cystoscopy per year, and up to 10% have no follow-up cystoscopies between 6 months and 3 years following diagnosis. Various patient factors are associated with low-intensity surveillance cystoscopy, but physician characteristics may also play a role.

For muscle invasive cancers that are usually managed with cystectomy, regular liver and renal function tests, and chest and abdominopelvic imaging, are also included in follow-up. Stage-specific post-cystectomy follow-up schedules have been suggested by others, with closer follow-up for higher stage tumors that are at increased risk of recurrence.[4,13]

Transurethral resection in staging of bladder cancer

The manner in which endoscopic resection is performed determines the accuracy of staging. It is known that there is a substantial risk of both over- and under-staging, from comparison of endoscopic results to cystectomy specimens. Overstaging occurs in up to 25% of cases and understaging in up to 50%.[14] The UICC specifies that for proper assignment of the T category, a transurethral resection of a bladder tumor (TURBT) should involve resection of all gross tumor, followed by a separate resection of the deep and lateral margins.[15] This has been recommended by others as well.[9,16] If the second separately submitted specimen of the margins shows no evidence of tumor, this demonstrates that the tumor was completely resected. Furthermore, because the depth of the deep margin is known with certainty using this approach, a pathologic T category can be assigned, just as it would if cystectomy had been performed. If the margins are not sent separately, only a clinical T category can be assigned.

In the case of T1 lesions, many advocate a second

resection 1-6 weeks post TURBT in order to improve staging accuracy and to ensure complete resection. It is known that there is a 33%-75% chance of finding tumor on re-resection, resulting in upstaging in 5%-29% of cases.[17-20] The probability of upstaging increases to 62% if no muscle was present in the initial resection specimen.[21] What is unclear is whether re-resection is necessary if the deep and lateral margins were sent separately during the original TURBT, as required by the UICC, and these were found to be free of tumor. Some believe that in this situation re-resection is unnecessary, while others suggest that the risk of finding residual tumor is still sufficiently high as to justify another procedure.[16]

Handling of tissues by surgeons is another area that may impact on staging accuracy.[22] Crush and cautery injury can result in an inability of the pathologist to accurately assess depth of tumor penetration, presence of muscle in the specimen, or occasionally even make a diagnosis of neoplasm when it is small.[23] Use of a pure cut current and movement of the loop rapidly through the tissue may help to minimize burn artefact. Surgeons must also handle resected tissue delicately, and avoid crushing specimens with forceps.

Pathologic examination of transurethral specimens

Clinicians and pathologists need to have good communication; clinicians must be able to interpret their colleagues' pathology reports accurately. Pathologists may sometimes report an absence of urothelium in the specimen (denudation). This diagnosis should alert clinicians to the possible presence of carcinoma-in-situ (CIS) in which the urothelium has been shed.[24] Diagnosis of urothelial carcinoma is not possible without the presence of urothelium, however. Thus, clinicians must be aware of the need for gentle repeat biopsies in an effort to establish the diagnosis, particularly when there is a high level of suspicion such as in cases where patients have positive urinary cytology or a history of CIS.[25]

Clinicians also need to be aware of some difference in the use of the terminology "invasive" when used by urologists versus pathologists. For urologists, "invasive" cancer usually implies muscle invasive cancer (i.e. T2 and higher in the 2002 TNM system). However, pathologists usually use the term "invasive" to indicate tumors that have breached the basement membrane and invade lamina propria (i.e. T1 and higher tumors). Clinicians must therefore be careful to read the detailed description in the pathology report in order to correctly interpret the stage of a tumor and hence make correct management decisions.

There are certain common errors that can be made by pathologists attempting to interpret TURBT specimens, and clinicians need to be cognizant of these. The muscularis mucosa is a discontinuous layer of wispy smooth muscle within the lamina propria. It is present in 50% of specimens and can be mistaken for muscularis propria.[26-28] Similarly, adipose tissue is present in the lamina propria in over 50% of cystectomy specimens, and in the muscularis propria in 100%.[29,30] This can be mistaken for perivesical fat, resulting in potential overstaging.

Lymphadenectomy in staging of bladder cancer

Surgical technique during radical cystectomy has garnered attention lately, particularly regarding the issue of lymph node dissection. There is evidence that patients have improved prognosis with greater numbers of lymph node removed.[31] It is thought that there is a therapeutic benefit to removing nodes containing metastases.[32]

However, it is also known from other tumor sites that examining more nodes increases the likelihood of proper staging.[33] This may lead to an apparent improvement in prognosis simply due to more accurate assignment of pathologic nodal (pN) category. In bladder cancer, node-negative patients who have greater numbers of nodes removed during cystectomy have a better prognosis than patients with fewer nodes excised.[34] In addition to the possibility that this is due to removal of nodes containing undetected micrometastases, this phenomenon may occur because there is an increased likelihood that the assigned pN0 status is accurate in patients with more lymph nodes removed, compared to patients in whom this status is assigned on the basis of only a few examined nodes.

There is not, at this point, consensus regarding the minimum number of nodes that should be examined for accurate assessment of pN status. The UICC has stated that eight or more lymph nodes should be assessed,[15] but others have suggested that larger minimum numbers are needed.[35]

The number of nodes obtained during radical cystectomy depends on a number of variables. The boundaries used in performing lymphadenectomy are one factor; more extended dissection results in improved nodal yield.[36,37] Other surgeon-specific factors may also play a role.[38] The use of separately submitted nodal specimens, rather than their inclusion en bloc with the cystectomy specimen, has been found to increase the number of nodes identified.[37,39] Finally, the effort made by the pathologist to look for nodes within submitted tissues, and use of techniques such

as fat-clearing solution also impacts on the number of nodes examined.[40]

Fluorescence cystoscopy

Because of the difficulty in identifying flat urothelial cancers such as CIS on cystoscopy, other methods for more accurately diagnosing the location of these tumors have been sought. Fluorescence cystoscopy is emerging as a potential technique for improving visibility of lesions that may otherwise be missed. It is performed using intravesical instillation of an agent with greater affinity for cancer cells compared to nonmalignant urothelium, such as aminolevulinic acid (5-ALA) and hexyl aminolevulinate (HAL). Intravesical rather than systemic administration significantly reduces the risk of systemic toxicity.[41] Following instillation, there is transient accumulation of Protoporphyrin IX, a metabolite with fluorescing properties. Under blue light, fluorescence occurs, and this results in increased contrast between malignant tissue that takes up more of the metabolite and benign tissue, which demonstrates less fluorescence.

A number of studies have examined the ability of fluorescence cystoscopy to aid with identification of urothelial lesions. Use of fluorescence cystoscopy has been reported to result in detection of more lesions compared to standard cystoscopy; it appears to be particularly useful for detecting CIS.[42] The improved sensitivity does come at the expense of diminished specificity, however, as more lesions such as inflammatory changes are detected also. In the literature, sensitivity of fluorescence cystoscopy ranges from 76%-97% and specificity from 33%-95%.[43]

The potential benefit of improved detection has been demonstrated in several clinical trials. Additional findings from fluorescence cystoscopy resulted in a change in patient management for up to 20% of patients.[44,45] Additionally, the use of fluorescence cystoscopy during the initial resection has been shown to reduce the rate of residual tumor on re-resection, and decrease the probability of tumor recurrence.[46-49]

Virtual cystoscopy

Virtual cystoscopy is being developed with the aim of decreasing the need for an invasive diagnostic and surveillance modality. In virtual cystoscopy, the bladder is filled with gas or fluid, and then images are acquired by CT or MRI. A computer program is used to render the images into a three-dimentional format. The computer software permits the user to "navigate" through the bladder, thereby simulating conventional endoscopy.[50]

The major disadvantage at the present is that tumors less than 5 mm may be missed with this technique.[51] Furthermore, both transverse and virtual images may be necessary, as small lesions are not well seen on standard images, and wall thickening is not easily visible on virtual imaging.[52] Newer techniques to measure bladder thickness may obviate the need for axial images in the future.[53]

Positron emission tomography

Positron emission tomography (PET) is a metabolic imaging tool that holds promise for imaging neoplasms. It is performed by intravenous injection of a labeled tracer, such as the 18 fluorine-labeled glucose analogue, 2-fluoro-D-deoxyglucose (FDG). FDG is taken up by cancer cells because they have an increased rate of glycolysis; because the tracer does not proceed along the usual metabolic pathway, it becomes trapped within the cells. Consequently, it accumulates more in malignant tissue, and produces a detectable signal.[54] This preferential labeling of cancerous tissue may aid in distinguishing reactive from malignant lymph nodes, and detecting foci of disease recurrence.

PET has shown utility in a number of primary cancer sites. In bladder cancer, the usefulness of FDG-PET has proven limited thus far.[55] This is because there is renal excretion of FDG, resulting in accumulation of the excreted tracer in the bladder. This makes it difficult to pinpoint the presence of bladder cancer within the bladder. It may be easier to identify recurrent disease after cystectomy. Work is being done to improve PET for use in bladder cancer, such as by the use of other PET tracers without renal excretion such as 11C choline, and by combining PET with CT imaging.[56]

Ultrasmall superparamagnetic iron oxide MRI

Ultrasmall superparamagnetic iron oxide (USPIO) MRI is a promising technique for imaging lymph node metastases. Ferumoxtran-10 particles are injected intravenously and are then transported via lymphatics into lymph nodes, where they are internalized by macrophages within the nodes.[57] Iron-loaded macrophages cause decreased signal intensity on T2-weighted MRI. Since metastases do not take up particles, metastatic areas retain a high signal intensity; metastatic nodes therefore demonstrate either no decrease in signal intensity or have a heterogeneous decrease in the signal.[58] The performance of USPIO MRI in bladder cancer has been reported to be superior to conventional MRI in terms of accuracy and sensitivity, albeit with slightly lower specificity.[59]

Summary

The clinical and radiologic techniques that are used in bladder cancer staging and follow-up continually undergo change. The TNM staging system itself evolves with time, and clinicians need to remain current in order to ensure staging accuracy. Clinical protocols are being developed based on the best available evidence, which should help to ensure appropriate utilization of staging and surveillance technologies. Knowledge is accumulating regarding optimal surgical and pathologic techniques for TURBT and lymphadenectomy, and this is expected to improve diagnostic accuracy and likely patient outcomes as well. Further development of new technologies such as fluorescence cystoscopy, virtual cystoscopy, PET, and USPIO MRI are anticipated to continue to improve the staging and surveillance of bladder cancer patients. □

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